INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0204 PRINCIPAL INVESTIGATOR: William Dahut, M.D.

STUDY TITLE: A Phase I and Randomized Phase II Multicenter Study of Cabozantinib (XL184) Plus Docetaxel and Prednisone in Metastatic Castrate Resistant Prostate Cancer

Continuing Review Approved by the IRB on 02/21/17
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

Cabozantinib is an agent that slows down the growth of blood vessels that feed tumors. Although it has been approved by the Food and Drug Administration to treat medullary thyroid cancer, it has not been approved for prostate cancer and its use in this study is experimental. Early studies have also shown that prostate tumors respond to cabozantinib. However when cabozantinib was taken alone, it did not shrink prostate tumors better than standard FDA approved therapies. In this study we will be investigating how cabozantinib works in combination with the FDA approved standard chemotherapy regimen of docetaxel and prednisone in people who have been diagnosed with metastatic (distantly spread) prostate cancer.

First we will try to establish safe doses for these drugs when they are taken together. We also hope to understand whether cabozantinib given together with docetaxel works better to treat distantly spread prostate cancer than when docetaxel is given alone.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have been diagnosed with progressive metastatic prostate cancer.

How many people will take part in this study?

Up to 81 subjects will be enrolled in this study.

Description of Research Study

This study consists of 2 phases. In phase I, all patients received cabozantinib in combination with docetaxel. We started with a low dose of cabozantinib (as described at the end of this section below) and gradually increased the dose until we found the highest dose that people could take safely.

Now we want to study if adding cabozantinib to docetaxel will result in a better outcome. In phase II, you will be randomized (like flipping a coin) to receive either cabozantinib in combination with docetaxel or docetaxel only.

Before you begin the study:

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. However, there are some extra exams, tests and procedures that you will need to have if you take part in this study. If you have had some of them recently, they may not need to be repeated.

These tests include:

- 12-lead electrocardiogram (ECG)
- Blood and urine tests
- CT scan (chest, abdomen and pelvis) and a bone scan

You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements. Some medications may interact adversely with cabozantinib and it is important that your study doctor and prescribing physician be aware of any potential risks so that they can prescribe alternative medications as necessary. If you do not already do so, please consider carrying a list of your medications at all times.

During the study:

If the results show that you can be in the study, and you choose to take part, then you will need the following tests and procedures:

- Dental examination (if you have used or are using a type of medication called a bisphosphonate) – before you receive study drug

You will need the following tests and procedures that are part of regular cancer care.

These tests will be done day 1 of each cycle.

- Blood tests
- Examination by a doctor

These tests will be done on day 1 of each cycle

- Urine tests
- ECG

You will also need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Bone scan and CT scan every 3 cycles

You will need blood and urine tests for research to see how the drug is affecting your body and for other research studies. These tests will be done:

- After you have enrolled but before you receive any study drug
- Before you receive the study drug on the following days: Day 1 of cycles 1, 2, 3, and 5
- After you receive the study drug at seven timepoints up to 24 hours after the first dose on day 1 on cycles 1 and 2, if you are enrolled to phase I or assigned to receive cabozantinib during phase II

You will be provided with a wallet-sized information card ("Information on Possible Drug Interactions") that names your study agent and outlines the specific risk of adverse interactions with other drugs or substances. Should you require any new medications while on study, please consult with your study doctor if possible, and present the card to the prescriber (doctor, pharmacist, physician's assistant, or nurse practitioner). Please check with your doctor/prescriber or pharmacist before using any new over-the-counter medications or herbal supplements.

You will need to be admitted to the hospital for the first 2 days of cycle 1 and 2 so that we may collect blood samples from you. After that, you will receive the medications in this study as an outpatient.

You will be given docetaxel through an IV catheter (a plastic tube usually inserted in a vein on your arm) on day 1 of each cycle. Each docetaxel infusion will take about 1 hour. You will also be asked to take prednisone by mouth twice each day of each 21 day cycle. You should take prednisone at around the same time every day with the doses approximately 12 hours apart, give or take two hours. Prednisone should, if possible, be taken with food or milk to reduce stomach irritation. If you vomit or miss a dose of prednisone, that is, if more than 14 hours have passed since the previous dose, you should not make up that dose. Instead, you should resume taking the drug at the next scheduled dose.

You will also take an assigned dose of cabozantinib by mouth in combination with the agents described above. The study team will tell you when you should take this dose. Cabozantinib should be taken on an empty stomach (no food should be eaten 2 hours before taking cabozantinib and1 hour after taking cabozantinib) and the pills should not be chewed or crushed. If you miss a dose or vomit, do not make up that dose even if you think you saw it come out. Instead, you should resume taking the drug at the next scheduled dose.

In Phase I of the study, you will be given docetaxel in combination with cabozantinib. If you are enrolled to Phase II of the study, you may or may not receive cabozantinib.

At each study visit, we ask that you bring all remaining cabozantinib tablets with you.

During Phase I of the study, 3 - 6 people will be enrolled and will take a 20 mg dose of cabozantinib once each day of each 21 day cycle. This is dose level 1. Based on how people tolerate the medication, the dose may be reduced for the next group of people enrolled or it may be increased. We will continue to enroll people until we find the highest dose that 6 people can take with only 0 or 1 experiencing intolerable side effects. We will then enroll 6 additional people to the study at that dose to obtain additional safety information about the combination therapy and to begin to find out how well the combination therapy works.

In a second phase of the study we will enroll some patients who will be assigned to receive docetaxel only and some patients who will receive docetaxel and cabozantinib together. Patients will be randomly assigned (like flipping a coin) to receive one of the two regimens. You will have an equal chance of being assigned to one of the two regimens.

Unless you experience serious side-effects or your disease progresses (gets worse), there is no limit to the number of cycles you may remain on the study regimen. Therapy may be stopped, however, for any of the reasons listed in the stopping therapy section below.

We ask that you:

- **avoid eating or drinking grapefruit and grapefruit products including grapefruit juice as well as Seville oranges and their products while enrolled on study as this may adversely interact with cabozantinib. Please read the product label as some products may contain grapefruit without your knowledge.**

- **discuss any planned dental procedures with the study team if you are taking or have taken in the past a type of drug called a bisphosphonate (e.g. alendronate, risedronate, pamidronate, etc.). Patients taking bisphosphonates and cabozantinib are at higher risk for a complication that may lead to the destruction or death of the jawbone.**

You may take antacids and other medications used to treat indigestion with **the exception of cimetidine**. Please let the study staff know, if you have been taking cimetidine. You may take an alternative medication for the duration of the study. Please discuss these options with the study doctor.

When you are finished taking the study drugs (treatment)

After you have taken your last dose of cabozantinib, we will conduct an end of study assessment. At this time, you will have a brief examination, your blood and urine will be tested and you will have an ECG. This assessment can be done any time within 30 days after you have completed treatment. After you finish study treatment, your local doctor will provide your cancer care.

Stopping Therapy

Your participation in this study will continue until either you or your study team decides that this medication is not beneficial to you. Your participation is voluntary; so you may stop receiving the study drugs at any time, but we ask that you speak to your study team before stopping. Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease progresses during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if you are unable to comply with the protocol requirements
- if you are unable to tolerate the lowest dose of cabozantinib (20 mg once every other day)
- if your treatment has been delayed for more than 2 weeks and it is not clear that you have been benefiting from cabozantinib

In this case, you will be informed of the reason therapy is being stopped.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Exelixis or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Birth Control

Because the effects of cabozantinib in combination with docetaxel and prednisone on the developing human fetus are unknown, men participating in this study must agree to practice an effective form of birth control before starting study treatment, during study treatment, and for 4 months after you finish study treatment. If you think that your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

You should recognize that no method of birth control besides abstinence provides 100% protection from pregnancy.

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The medications used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. The docetaxel which is used in this study also contains ethanol or alcohol which may cause you to feel drunk during or after treatment. It

may be necessary to avoid driving, operating any machinery or performing any activities that are dangerous for one to two hours after the infusion of docetaxel. Some medications such as pain relievers or sleep aids may interact with the alcohol in docetaxel and may worsen these effects.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Cabozantinib

COMMON, SOME MAY BE SERIOUS In 100 people receiving XL184, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite • Changes in taste or voice • Redness, pain or peeling of palms and soles • High blood pressure which may cause blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving XL184, from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Constipation, heartburn • Dry mouth, skin

- Sores in mouth which may cause difficulty swallowing
- Swelling of arms, legs
- Infection
- Bruising, bleeding
- Dehydration
- Muscle spasms
- Dizziness, headache
- Kidney damage which may require dialysis
- Cough, shortness of breath
- Internal bleeding which may cause coughing up blood, black tarry stool or blood in vomit
- Bleeding from multiple sites including the nose
- Hair loss, rash
- Change in hair color
- Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS

In 100 people receiving XL184, 3 or fewer may have:

- A tear or hole in internal organs that may require surgery
- Non-healing surgical site
- Damage to the jawbone which may cause loss of teeth
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)

Docetaxel

COMMON, SOME MAY BE SERIOUS In 100 people receiving Docetaxel, more than 20 and up to 100 may have:
• Swelling of the body • Hair loss • Change in nails • Rash, itching • Vomiting, diarrhea, nausea, constipation • Sores in mouth which may cause difficulty swallowing • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Tiredness • Numbness and tingling of the arms and legs • Fever • Absence of menstrual period • Swelling and redness of the arms, leg or face • Pain • Watering, itchy eyes

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Docetaxel, from 4 to 20 may have:
• Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body • Belly pain • Bruising, bleeding • Liver damage which may cause yellowing of eyes and skin • Kidney damage which may require dialysis • Blood clot which may cause swelling, pain, shortness of breath • Abnormal heart rate • Shortness of breath, wheezing • Chest pain

RARE, AND SERIOUS In 100 people receiving Docetaxel, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Cancer of bone marrow (leukemia) caused by chemotherapy • Scarring of the lungs

Prednisone

COMMON, SOME MAY BE SERIOUS In 100 people receiving Prednisone, more than 20 and up to 100 may have:
• In children and adolescents: decreased height • Loss of bone tissue • Mood swings • Skin changes, acne • Swelling of the body, tiredness, bruising • High blood pressure which may cause headaches, dizziness, blurred vision • Pain in belly • Increased appetite and weight gain • Weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Prednisone, from 4 to 20 may have:
• Cloudiness of the eye, visual disturbances • Glaucoma • Infection • Non-healing wound • Diabetes • Damage to the bone which may cause joint pain and loss of motion • Kidney stones • Heartburn

RARE, AND SERIOUS In 100 people receiving Prednisone, 3 or fewer may have:
• Bleeding from sores in the stomach • Broken bones

Potential Benefits of Participation

Are there benefits to taking part in this study?

We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- The study agents, cabozantinib, docetaxel and prednisone will be provided by the NCI. You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will my medical information be kept private?

Your privacy is very important to us and we will make every effort to protect it. Your information may be given out if required by law. However we will do our best to make sure that any information that is released will not identify you.
There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The study sponsor
- The Food and Drug Administration (FDA)
- The drug company supporting the study.
- The local Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who participate in the study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about clinical trials or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug, cabozantinib, developed by Exelixis through a joint study with your researchers and the company. The company also provides financial support for this study to the NIH.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

Some of these studies may be about genes. Genes carry information about features that are found in you and in those who are related to you. Researchers are interested in how genes affect health and disease, and how genes affect how your body responds to treatment.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, William Dahut, M.D., Building 10, Room 3-2571, Telephone: 301-435-8183. You may also call the Clinical Center Patient Representative at (301) 496-2626. If you have any questions about the use of your tissue for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____

Signature of Adult Patient/ Legal Representative Date

_____

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

_____

Signature of Parent(s)/Guardian Date

_____

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

_____ _____

Signature of Parent(s)/Guardian Date Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 21, 2017 THROUGH FEBRUARY 20, 2018.

_____ _____

Signature of Investigator Date Signature of Witness Date

_____ _____

Print Name Print Name